REMARKS

Claims 3-5, 7, 9, 10, 27-30, 33-37, and 52-60 are pending and under examination. Claims 4,7, 10, 27, 33, 35, 36, 37, 54, 57, and 58 have been amended. Claims 5, 9, 28-30, 34, 52, 53, 55, 56, 59 and 60 have been cancelled without prejudice to pursuing the subject matter in the future.

Several amendments have been made to the claims. Support for the amendments to the claims can be found in the specification. For example, the independent claims have been amended to incorporate the subject matter of claims 5 and 60 (i.e. reciting covalent linking of oligonucleotides to the first substrate according to claim 5 and reciting that the pool of oligonucleotides comprises greater than 50 oligonucleotides according to claim 60) support for which can be found, for example, at page 9, line 2.

In view of this amendment, other amendments have been made to the independent claims and several dependent claims for consistency and proper antecedent relationships, for example, by replacing the phrase "at least first and second" with the term "different." For the two substrates in each independent claim, one bearing the oligonucleotides attached through the cleavable linker and the other bearing the probe sequences, claims have been amended to recite "first substrate" and "second substrate" to correct antecedent basis. The claims have also been amended to recite "wherein said first substrate comprises an array of discrete sites to which said different oligonucleotides are linked" support for which can be found, for example at claim 7; page 17, lines 9-14 and page 21, lines 15-21.

New claims 61-74 have been added. New claim 61 is supported by Figure 3 and claims 28 and 34 which have been canceled in this amendment. Claim 61 restates claims 28 and 34 for the purpose of clarity. New claims 62-67 find support in incorporated references. Specifically, support for "greater than 2000" is found in USPN 5,700,637 at column 7, lines 23-31. Support for greater than 1000 is found in USPN 5,807,522 at column 13, lines 10-20 and column 14, lines 19-21. Support for greater than 400 is found in USPN 5,807,522 at column 14, lines 21-23 and Figure 5. New claims 68-72 recite individual elements of the Markush group previously recited in claim 58. Similarly the Markush group previously recited in claim 57 has been broken out into separate claims by amendment of claim 57 and addition of new claim 73. New claim 74

has been added, support for which can be found, for example, at page 3, lines 12-17; page 6, lines 11-13; and page 8, lines 14-18.

Accordingly, these amendments and new claims do not raise an issue of new matter and entry thereof is respectfully requested. Following entry of the amendment claims 4, 7, 10, 27, 33, 35, 36, 37, 54, 57, 58, and 61-74 will be pending.

Applicants have reviewed the Office Action mailed February 21, 2008, and respectfully traverse all grounds of rejection for the reasons that follow.

Regarding the Interview on June 3, 2008

Dr. John Stuelpnagel, co-inventor and co-applicant, and Applicants' representatives wish to thank Examiner Strzelecka for meeting on June 3, 2008, and for the thoughtful and courteous discussion of the pending claims, cited art and potential amendments. In particular, amendments relating to the number of amplified targets and primer optimization were discussed. In particular, a distinction was made between the cited art of record and the invention as reflected in the claims pending at the time of the interview. Specifically, Applicants' representatives detailed how each of the secondary references teaches a need to optimize individual primer designs and primer concentrations requiring labor intensive verification that each primer will perform properly in multiplex amplification. By contrast, in the present claims, the plurality of oligonucleotides released from the substrate can be used analogously in multiplex amplification "as is," with no need for adjustment of primer concentrations. With regard to Applicants' claimed methods, creating a pool and subsequently expending the time and resources to purify primers from the pool for individual optimization only to ultimately reconstitute a pool would be purpose-defeating and inefficient. In order to capture this advantage of the invention more clearly in the claims, the claims have been amended to recite that the same 50 primers that are in the released pool are the same ones present and used in the subsequent steps. Overall, Applicants submit that the amendments made herein address the issues discussed in the interview and the outstanding rejections.

Double patenting

Claim 55 is objected to under 37 C.F.R. 1.75 as being a duplicate of claim 28. The double patenting objection to claim 55 has been rendered moot by cancellation of claim 55. Withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. §103-Pastinen and Lipshutz as evidenced by Sinha, Weiler, Shuber and Wang

Claims 5, 7, 9, 10, 27-30, 33-37, 53, 55, and 57-60 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pastinen et al. and Lipshutz et al. as evidenced by Sinha et al. Weiler et al., Shuber et al. and Wang et al. as set forth in the Office Action in item 11.

Regarding claims 5, 9, 28-30, 34, 53, 55, 59 and 60, their cancellation set forth in this amendment renders this rejection moot.

The following argument applies to independent claims 27, 33, and 35 and therefore apply equally to their corresponding dependent claims 7, 10, 36, 37, 57, and 58.

In the response to the Applicants' arguments, the Examiner disagrees with Applicants' assertion that one skilled in the art would not have had a reasonable expectation of success in combining the references to arrive at the claimed invention. The Examiner states that "the problem is not whether the pools are created by the method of Lipshutz et al. or by mixing together individually synthesized primers, but whether the primers are designed in a way which would ensure that they would work together in a highly multiplexed amplification reaction, the problem which has nothing to do with the way they are synthesized." Office action item 6 at page 4, last paragraph through top of page 5. Based on the Office Action, the Examiner appears to believe that the problem is merely one of primer design. During the interview on June 3, 2008, this concern was clarified by Applicants' representatives by pointing out how each of the cited secondary references discuss the issue of optimizing primer concentration as a prerequisite for success of their methods. The relevant arguments discussed with the Examiner on June 3, 2008, are reiterated below on the written record.

The Examiner provided two references as allegedly supporting the position that the problem described in the seconday references is merely one of primer design. First the Examiner alleges that Shuber et al. designed a pool of 30 different primers for use in a multiplex amplification reaction. Second the Examiner alleges that Wang et al. also used primer design to amplify sets of 558 loci.

A review of the references provided by the Examiner shows that they are inconsistent with the position taken in the Office Action, and even refute this position. Specifically, although Shuber et al. does use primer design, they repeatedly teach that a key to the success of the multiplex amplification was optimization of primer concentration. Specifically, at the passages pointed to by the Examiner, Shuber et al. describe a multiplex amplification method in which the primers are at different concentrations (see the legend to Figure 2 and the section entitled "amplifications" on page 490). In describing the results of the multiplex reaction at the paragraph spanning columns 1 and 2 of page 491, Shuber et al. states that

> As demonstrated for exon 21 (Fig. 1), each chimeric primer pair concentration used within the CFTR 15-plex was determined by performing independent amplicon amplification over a range of concentrations (Fig. 2). Using the same amplification conditions that were originally defined for the individual chimeric primer pairs, all 15 of the predicted CTFR PCR products co-amplified with relative ease.

The importance of optimizing primer concentration is reiterated elsewhere in Shuber et al. For example, the abstract states that

> Under these conditions, efficient multiplex amplification is achieved easily and reproducibly by simple adjustment of the individual primer concentrations.

Similarly, the first paragraph of the Discussion includes the statement

> Highly specific and efficient amplification of target sequences can be achieved easily and reproducibly by simple adjustment of the individual primer concentrations, with no additional modification of either reaction components or annealing temperature.

These teachings of Shuber et al. do not support the assertion in the Office Action that "the problem here is not whether the pools are created by the method of Lipshutz et al. or by

mixing together individually synthesized primers." On the contrary, Shuber et al. suggests that individual synthesis is required such that the concentrations for primers can be optimized in individual reactions prior to being mixed together. In view of the teachings in Shuber et al. those skilled in the art would not have had a reasonable expectation of success that the oligonucleotides used for a multiplex PCR reaction could be obtained by the synthesis method of Lipshutz et al. because the Lipshutz et al. methods do not provide for the optimization of individual primer concentrations that are identified by Shuber et al. as being important to the success of the amplification.

The Wang et al. reference also describes a reliance on empirical assays using individual primers to optimize conditions prior to carrying out a multiplex amplification step. See the first paragraph on page 1080, and in particular the reference to footnote 25 which states that "[e]ach PCR primer pair was individually tested to determine if it produced a single clear fragment visible by agarose gel electrophoresis . . ." Again, by teaching a requirement to optimize primers in individual amplification reactions Wang et al. would not have provided one skilled in the art with a reasonable expectation of success that a pool of primers produced by the methods of Lipshutz et al., in which individual optimization of primer concentration is avoided, could be used in the methods of Pastinen et al. to arrive at the claimed invention.

The weight of evidence, including the teachings of Shuber et al. and Wang et al. (as set forth above) and the teachings of Pastinen et al. and Syvanen et al. regarding the challenges of multiplex PCR (as set forth in the previous response), supports Applicants' position that those skilled in the art would not have had a reasonable expectation of success in substituting the oligonucleotides produced by the method of Lipshutz for the individually synthesized primers used by Pastinen et al. to arrive at the claimed invention.

The claimed invention involves the generation of a pool of oligonucleotides by release of greater than 50 different oligonucleotides from a substrate and subsequent modification of the released oligonucleotides with no need to optimize the primers, in sharp contrast to the teachings of Pastinen et al., Syvanen et al., Shuber et al. and Wang et al.. As recited in the currently amended claims, the same 50 primers released to form a pool are used directly in subsequent steps. The art of record suggests that if one wanted to use the pool of Lipshutz one would have

to individually optimize each oligonucleotide for use in multiplex PCR, a notion entirely absent from the explicit or implied teachings of Lipshutz. Any advantage of generating a pool of oligonucleotides would have been lost if the individual oligonucleotides were isolated for optimization and then placed back into a pool. For at least these reasons the claims would not have been obvious.

In another attempt to establish reasonable expectation of success, the Office Action points to the Weiler et al. reference. Specifically, the Action alleges that Weiler et al. teaches a method of synthesizing oligonucleotides on polypropylene sheets and cleaving them to produce oligonucleotides having quality that produces the same results as commercially available primers, even without further purification. However, quality of oligonucleotides is not the only characteristic that one skilled in the art would have been led to consider. As set forth above, the art of record would have lead one of skill in the art to believe that control of individual primer concentration was important to achieve multiplexed amplification. Whether or not Weiler et al. describes their methods as producing good quality oligonucleotides, they describe their methods as producing oligonucleotides with variable yields. See for example, page 224, column 1, first full paragraph which states that "most of the oligonucleotide product was found to be full-length molecules indicating a stepwise coupling efficiency of more than 98.5%." In further consideration of the subsequent cleavage step Weiler et al. states "the amount of released oligonucleotide probe could be calculated to be more than 25 pmol/cm^2 polypropylene." Thus, Weiler et al. describes variable yields, giving no indication that the concentration of oligonucleotides produced in the solid phase synthesis methods would be known from the amount of material entering the synthesis, nor that oligonucleotides of different length or composition would have similar yields. Accordingly, there would not be a reasonable expectation that the Weiler et al. methods could be used to produce a pool of different primers, each at a known an optimized concentration for use in the multiplex PCR method of Pastinen et al.

Furthermore, Weiler fails to provide a significant PCR experiment, for example, with a large oligonucleotide pool, as recited in the newly amended independent claims. Weiler appears to only use two primers in the PCR experiment. See page 224, Figure 7. This is significant in light of established perception in the art of record of the complexities associated with carrying

out multiplex PCR. Accordingly, one skilled in the art would have expected that in order to know the concentrations of different oligonucleotides for use in a multiplex PCR reaction, the oligonucleotides would need to be released individually and evaluated individually prior to creating the pool as taught by Shuber and Wang. In view of the art of record, those skilled in the art would not have had a reasonable expectation of success that a pool of oligonucleotides produced by the methods of Lipshutz et al. could be used in the methods of Pastinen et al. to arrive at the claimed invention. Therefore, the claims would not have been obvious.

The remaining dependent claims should be patentable for at least the same reasons. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §103-Pastinen and Lipshutz as evidenced by Sinha, Weiler, Shuber and Wang and in further view of Nelson

Claims 3 and 4 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Pastinen et al. and Lipshutz et al. as evidenced by Sinha et al. Weiler et al., Shuber et al. and Wang et al., in further view of Nelson, as set forth in the Office Action in item 12.

Claims 3 and 4 are multiply dependent from independent claims 27, 33, and 35 discussed above. The argument regarding Pastinen, Lipshutz, Sinha, Weiler, Shuber, and Wang are applied as above. Further, Nelson fails to remedy the shortcomings of these references with respect to the independent claims. Because claims 3 and 4 depend from these independent claims they are patentable for at least the same reasons. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §103-Beattie and Lipshutz in view of Sinha and Weiler

Claims 3-5, 7, 9, 10, 27-30, 33-37, 53, 55, and 57-60 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beattie et al. USPN 6,268,147 and Lipshutz et al. as evidenced by Sinha et al. and Weiler et al. as cited above. Office Action at item 13, page 14.

Regarding claims 5, 9, 28-30, 34, 53, 55, 59 and 60, their cancellation set forth in this amendment renders this rejection moot.

The following argument applies to independent claims 27, 33, 35 and therefore apply equally to their corresponding dependent claims.

As a preliminary matter, Applicants reiterate that the rejection is improper because the cited Beattie et al. reference (US 6,268,147) is not prior art, having been filed after the filing date of the instant application. The Examiner continues to rely on the '147 patent based on its priority claim to a provisional application having an earlier filing date. Specifically, the Examiner has asserted at pages 5-6 of the Office Action that "all of the matter relied on in the rejection is presenting the priority application 60/106,655" and has pointed Applicants to the PAIR record for the application. Applicants have briefly reviewed the PAIR record and have found that indeed not all of the subject matter relied upon by the Examiner is present in the '655 application. Specifically, the description of ligation at column 12, lines 47-67, relied upon by the Examiner as satisfying the modification step of the claims is not present in the '655 application. In fact, the entire section of the cited '147 patent spanning from column 12, line 28, through column 13, lines 45 is missing in the '655 provisional application.

Applicants further submit that even if the description of binding in '147 were to be present in a reference filed prior to Applicants' filing date, it does not meet the step of modifying as recited in the claims. First, the mere binding of an oligonucleotide to a capture probe does not constitute a modification of the oligonucleotide because this does not cause a change in the covalent structure of the oligonucleotide. Second, the claims recite, *inter alia*, ". . . modifying said different oligonucleotides . . . to produce modified oligonucleotides . . ." and ". . . contacting said modified oligonucleotides with a substrate . . ." Applicants do not disagree that the claims can encompass embodiments where these two events are preformed simultaneously. However, here the claims recite two events and the '147 patent only provides one. More specifically, even assuming *arguendo* that binding an oligonucleotide to a probe as described in the '147 patent could be considered to satisfy the "modifying" event recited in the claims, the '147 patent is deficient in not describing the second "contacting" event. In other words, a single event described in the cited reference cannot satisfy the requirement for two events in the claims, even if a term used in the cited reference is considered to be synonymous with two terms used in the claims.

Furthermore, even if the combination of references were to teach or suggest all elements of the claims, one skilled in the art would not have been motivated with a reasonable expectation of success to modify the method of Beattie et al. to include the pools of Lipshutz et al. Weiler et al. would not cure the deficiency because Weiler performs amplification with only 2 primers. Also, as shown above, the cited art of record, namely Shuber and Wang, teach that multiplex PCR success is dependent upon primer optimization, whereas in the instant claimed invention, such a need is obviated. The claims have been amended to recite generating a pool of greater than 50 different oligonucleotides. As such, the claims require, *inter alia*, that a pool of greater than 50 different oligonucleotides is released from a substrate, contacted with different target nucleic acids, modified and contacted with a substrate having probes. The references taken alone or in combination do not teach or suggest such a method because those skilled in the art would not have had a reasonable expectation that a pool of 50 different oligonucleotides could be used in the methods of Beattie et al. in the way alleged by the Examiner, at least for the reasons set forth above in regard to the rejection of the claims over Lipshutz et al. in view of Pastinen et al. Accordingly, the claims would not have been obvious. The remaining claims under this rejection depend from independent claims 27, 33, and 35 and should therefore be patentable for at least the same reasons. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. §103-Beattie and Lipshutz in view of Sinha and Weiler and in further view of Walt and Michael

Claims 52, 54, and 56 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Beattie et al. and Lipshutz et al., as evidenced by Sinha et al. Weiler et al. as cited above and in further view of Walt et al. USPN 6,327,410 and Michael et al. (Anal. Chem. vol. 70, pp. 1242-1248, April 1998). Office Action at item 14, page 21.

Regarding claims 52 and 56, their cancellation set forth in this amendment renders this rejection moot.

Regarding claim 54, the arguments presented for patentability over Beattie et al. and Lipshutz et al., as evidenced by Sinha et al. and Weiler et al. are applied as above in independent claims 27, 33, and 35. Walt and Michael fail to make up for their deficiencies. Withdrawal of this rejection is respectfully requested.

Entry of the proposed amendments is respectfully submitted to be proper because the amendments are believed to place the claims in condition for allowance.

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

Without addressing the merits of the rejections set forth in the Office Action mailed February 21, 2008, Applicants have canceled claims 5, 9, 28-30, 34, 53, 55, 59 and 60 without prejudice to Applicants pursuing these claims in a related application.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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